

Remarks

Applicant submits the following Remarks for consideration.

Rejection Under 35 U.S.C. § 112 First Paragraph

The Examiner has rejected claim 70 under 35 U.S.C. § 112 first paragraph for allegedly containing subject matter not described in the specification. Support for the membrane module having internal spaces and a gas outlet in an internal space can be found throughout the specification including on page 5 lines 27-35. Also, page 6 lines 1 - 9 and as depicted in Figure 3 that is described on page 12 lines 20 - 36. Applicants respectfully request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 112 Second Paragraph

Claim 45 was rejected under 35 U.S.C. § 112 second paragraph for purportedly being unclear by requiring supplying the dialysis fluid space or the culture fluid space with the second gas when claim 45 is dependent on claim 39 where the second gas is introduced in the culture fluid space of the module. Claim 39 recites introducing a second gas into the culture fluid in the culture fluid space in the membrane module with no distinction as to direct or indirect delivery method. Claim 45 recites "directly introducing the second gas". Support for direct and indirect methods of introducing gas is found throughout the specification. For example, page 8 lines 1 - 34. Accordingly, withdrawal of this rejection is respectfully requested.

Claim 70 was rejected under 35 U.S.C. § 112 second paragraph for allegedly being indefinite for failing to point out and distinctly claim the subject matter. Claim 70 requires the dialysis membrane to have internal spaces and a gas outlet in one of the internal spaces. Since membranes are normally thin with internal spaces too

small to accommodate a gas inlet/outlet, one embodiment of the invention is for the membrane to have the shape of a tube and for its volume to form one of the two spaces of the membrane module. Support for this embodiment is found in the specification on page 5 lines 34-35, page 6 lines 1 - 9 and is depicted in Figure 3 with corresponding description on page 12 lines 20 - 36. Thus, withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. § 103

Claims 39-50, 52-70, 81,82 and 84-92 are rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Pörtner et al. The Examiner contends that "it would have been obvious to supply air to space containing circulating culture liquid containing cells in the dialysis module of the reactor of Figure 2a of Portner et al. to prevent cells from suffering oxygen limitation as disclosed on page 404 since it would have been apparent from Figure 3a that oxygen can be supplied to cells in a chamber separated from a dialyzing chamber by a dialysis membrane". Reconsideration of this rejection for the following reasons is respectfully requested.

First, the conditions claimed by the instant invention are not simply conditions that would be expected to be matters of optimization when using the reaction system of Pörtner et al by one skilled in the art. Applicant is not aware of any dialysis module on the market that is equipped with means to supply air to the cells. Furthermore, there is no dialysis module on the market that can easily be modified in such a way to supply gas to the cells because standard dialysis modules available usually contain tubular membranes with an inner diameter of 1 mm or smaller. In such modules, there is no space to insert a means to supply gas to the cells. Thus, for the instant invention to have been obvious, tubular membranes with an appropriate inner diameter or a port to deliver gas in standard dialysis modules would have to have been readily available. It was generally believed that aeration of dialysis modules of the type shown in Figure 2a of Pörtner et al. was not possible. Although Pörtner et al. discloses the problem that cells in the dialysis module are suffering from oxygen

limitation, there is no hint or suggestion for finding a technical solution to the problem.

Furthermore, appropriate dialysis membrane modules were not available in the art and the instant invention recognized the utility membrane modules structurally designed specifically for hemodialysis (page 22 lines 4- 31 of the instant specification). While it was known these membranes were useful for removing toxic metabolites, it was not known these membranes could be utilized for gas delivery. The instant application provides this knowledge to one skilled in the art (see page 18 line 36 continuing to page 22 line 35).

Second, providing air to the dialyzing chamber as required by certain claims of the instant invention would not have been suggested by Figure 3b of Pörtner et al. In Figure 3b of Pörtner et al., a membrane dialysis reactor is described for cultivating mammalian cells. Air is provided to the dialyzing chamber. In this system, the cells in the culture chamber are supplied with oxygen via the dialysis membrane. It is well known in the literature that animal cells can be aerated via membranes due to their low oxygen requirements. In many of the known culture systems for animal cells, one can readily find membranes that are used to provide oxygen to the cells. For example, a typical membrane reactor was developed by Professor Lehmann (University of Bielefeld). He used tubular membranes that was capable of supplying $0.03 - 0.035 \text{ g}_{\text{oxygen}}/(\text{litre} \cdot \text{h})$ to the cells. But to accomplish this, he needed 2 meters of tubular membrane for 1 litre of culture fluid. In contrast, the instant application addresses the higher oxygen demands of a microbial culture of *E. coli* that is between 5 and $10 \text{ g}_{\text{oxygen}}/(\text{litre} \cdot \text{h})$. This is more than 100 times that required by animal cells. Thus, one skilled in the art can instantly recognize that microbial cultures with a high demand of oxygen cannot be supplied with oxygen via a membrane. There simply is not enough space in the reactor to introduce the necessary amount of membrane (200 – 600 m of tubular membrane in one litre of culture volume would be required). For this reason, it is generally believed that aeration via a membrane for microbial cultures such as *E. coli* is not possible because of technical limitations.

Further, the instant application does not specifically address supplying the culture chamber with gas, but focuses on the technical problem of oxygen limitation for the small amount of organisms that are outside in the externally located membrane module for a short time. As described in the instant application, sufficient oxygen supply is possible only when the volume that has to be supplied with oxygen is small compared to the membrane area available and the gas permeability of the membrane is high. The solution to the problem is not obvious from the information disclosed by Pörtner et al. The instant invention is based on the surprising finding that, with the technical means claimed, cells that are pumped through the external membrane module can be supplied with oxygen and do not suffer from oxygen limitation.

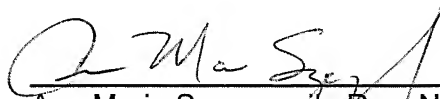
Third, *prima facie* obviousness does not exist without some reason given in the prior art as to why one of ordinary skill in the art would have been prompted to make such a modification. Pörtner et al. merely notes that the two-vessel approach encountered a problem with oxygen limitation (page 404) and goes on to describe an alternative approach using the one-vessel approach (page 404, 7th full paragraph). Indeed, the reference concludes with suggesting the two-vessel approach would only be applicable to cells with low oxygen requirement (page 412, 4th full paragraph). Given the aforementioned structural limitations, it would not have been obvious to add a gas supply to the membrane module. Hindsight cannot be used to deem the invention obvious when the inventors only had at their disposable the then-accepted wisdom of the field and typical "tools of the trade" at the time of the invention. Lacking any reason to make the modification provided by the prior art, the claimed subject matter of the instant application cannot be deemed to have been obvious.

For the foregoing reasons, withdrawal of the Rejection Under 35 U.S.C. § 103 is respectfully requested.

In view of the associated Remarks reconsideration and withdrawal of all outstanding rejections are deemed proper.

Applicants respectfully submit that the application is now in condition for allowance and request notice thereof.

Respectfully submitted,

A handwritten signature in cursive script, appearing to read "Ann Marie Szczepanik", written over a horizontal line.

Ann Marie Szczepanik, Reg. No. 52,267
Agent/Attorney for Applicants

sanofi-aventis U.S. LLC
Patent Department
Route #202-206 / P.O. Box 6800
Bridgewater, NJ 08807-0800
Telephone (908) 231-4658
Telefax (908) 231-2626
Docket No. DEAV1999/S009 US PCT